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Abstract

Amiodarone is the most effective rhythm-control for atrial fibrillation, but produces serious potential side effects. Dronedarone was designed to eliminate amiodarone toxicities, but increased the risk of mortality in clinical trials. This medication use evaluation compares one year of dronedarone use with a matched cohort of amiodarone patients at a single hospital in Greensboro, NC. Forty-eight patients were included with an average age of 71.8 years and 37.5% female population. No significant difference was found for the primary composite outcome of death, myocardial infarction, stroke, and systemic embolism (OR = 2.4, p = 0.148). Likewise, no statistical significance was demonstrated between the two groups for QTc prolongation, hypothyroidism, liver dysfunction or maintenance of normal sinus rhythm. In conclusion, the clinical decision process demonstrated no increased risk of death or other adverse events in the use of dronedarone.

Key Words: Dronedarone, Amiodarone, Medication Use Evaluation, Atrial Fibrillation

Introduction

Atrial fibrillation (AF), the most frequently diagnosed cardiac arrhythmia, affects 2 million American patients. The growing number of elderly patients is expected to further increase the rate of AF. AF increases a patient's morbidity and mortality through an increased risk in stroke, embolism and heart failure. Management of AF includes three angles of treatment including cardioversion, anticoagulation and rate control. Chemical cardioversion utilizes antiarrhythmic medications to maintain normal sinus rhythm by restoring the balance of ion channels in the cardiac muscle tissue.[1] The most effective drug of rhythm control, amiodarone, maintains normal sinus rhythm in 65% of patients within the first year.[2] However, amiodarone use is complicated by numerous side effects such as hepatic and pulmonary toxicities, changes in thyroid metabolism and other toxicities associated with long term use.[3]

Dronedarone was designed as the "non-iodinated benzofuran derivative" of amiodarone to expected to maintain efficacy and improve tolerability.[1] In the ATHENA Trial of 4600 patients, dronedarone decreased cardiovascular and arrhythmic death, but demonstrated no effect on all-cause mortality.[4] While originally thought to be a safer alternative to amiodarone, dronedarone has significant black box warnings and contraindications. Use of dronedarone remains limited to paroxysmal or persistent AF in patients without symptomatic heart failure.[5] These limitations were determined based on two clinical trials. In the ANDROMEDA trial, 627 patients with heart failure and no AF received dronedarone or placebo. The trial was terminated early as the risk of mortality doubled in the dronedarone group.[6] In PALLAS, patients with permanent AF had their trial stopped due to a doubling of the risk of stroke, clots, myocardial infarctions and death.[7]

Due to the concerning increased risk of mortality in multiple clinical trials, the use of dronedarone has decreased dramatically due to the limited indicated patient population. While amiodarone remains the most effective option, toxicities leave clinicians searching for a safer alternative. This retrospective, matched cohort study aims to determine the rate of adverse events in dronedarone use against matching patients receiving amiodarone in the clinical setting.

Methods

In this IRB-approved medication utilization evaluation, patients taking dronedarone and amiodarone were compared for serious adverse events, efficacy and readmissions. The study occurred at a single-center in Greensboro, North Carolina. All patients receiving an inpatient order of dronedarone during the calendar year 2015 were included. Matching amiodarone patients were chosen by selecting the same age, same sex and the nearest admission date to the dronedarone patient.

The data collected included that patient's age, and sex, date of admission(s), medications, death (and cause of death if applicable), myocardial infarction, stroke, symptoms of heart failure, most recent LVEF, electrocardiogram rhythm, QTc interval, and thyroid status.

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The primary objective of this study was the composite outcome of all-cause mortality, myocardial infarction, stroke and systemic embolism. Secondary objectives included each aspect of the primary composite individually, as well as cardiovascular mortality, maintenance of normal sinus rhythm, QTc prolongation greater than 450 milliseconds, liver toxicity assessed by either AST or ALT greater than 40 mg/dL, hypothyroidism, and number of readmissions within the next year of hospitalization.

Results

Between Jan 1, 2015 and December 31, 2015, dronedarone was ordered 40 times for 24 different patients. During the same period, amiodarone was ordered 2,682 times. Through matched cohort pairing, two groups of 24 patients were of the same average age (71.8 years) and the same distribution of males to females (37.5% female), as seen in Table 1. Patients in the dronedarone group had lower serum creatinine, were more likely to be on anticoagulation, and had fewer patients with symptomatic heart failure and reduced ejection fraction less than 35%.

Table 1. Patient Demographic Information

	Dronedarone	Amiodarone
Total Patients (n)	24	24
Age (years)	71.8	71.8
Sex (Female)	37.5%	37.5%
Serum Creatinine (mg/dL)	1.2	1.7
Anticoagulation	19	14
Symptomatic Heart Failure	3	14
LVEF ≤35%	2	11

In the primary outcome shown in Table 2, 5 dronedarone patients (20.8%) and 12 amiodarone patients (50.0%) experienced an outcome event of death, stroke, myocardial infarction or systemic embolism. The odds ratio of 2.4 showed a trend of reduction in events with dronedarone, but failed to meet statistical significance (p = 0.148).

For secondary outcomes, no comparisons reached statistical significance as some events trended to demonstrate benefit. Fewer patients died in the dronedarone group (3) compared to the amiodarone group (8), with an odds ratio of 2.67 (p = 0.183). No patients in the dronedarone group died of a cardiovascular cause, while 6 amiodarone patients met this criteria (OR = 13, p=0.086). Both groups had the same number of strokes (1 vs 1, OR = 1, p = 1) and a similar number of myocardial infarctions (1 in dronedarone vs 2 in amiodarone, OR = 2, p = 0.582). One patient on amiodarone experienced a systemic embolism compared to none in the dronedarone group (OR = 3, p = 0.508).

Both medications increased the QTc interval, with 9 dronedarone patients having a QTc ≥ 450 milliseconds and 17 amiodarone groups (OR = 1.89, p = 0.206). Both groups had four patients with elevated liver function enzymes (OR = 1, p = 1). Six dronedarone patients were diagnosed with hypothyroidism, while 9 amiodarone patients met the criteria (OR = 1.5, p = 0.5). In terms of efficacy, 14 dronedarone patients and 15 amiodarone groups were in normal sinus rhythm (OR = 1.07, p = 0.883). Patients in the dronedarone group were readmitted 1.7 ± 1.4 times during the next year, as 1.4 ±1.3 readmissions were seen in the amiodarone group (Difference 0.3, p = 0.446).

Table 2. Safety and Efficacy Comparison of Dronedarone Patients and Matched Cohort

	Dronedarone		Amiodarone		Odds Ratio	p Value
	Events	Percent	Events	Percent		
Composite of Death, Stroke, MI, and Embolism	5	20.8%	12	50.0%	2.4	0.148
All-Cause Mortality	3	12.5%	8	33.3%	2.67	0.183
Cardiovascular Death	0	0.0%	6	25.0%	13	0.086
Stroke	1	4.2%	1	4.2%	1	1
MI	1	4.2%	2	8.3%	2	0.582
VTE	0	0.0%	1	4.2%	3	0.508
Prolonged QT (>450 ms)	9	37.5%	17	70.8%	1.89	0.206
Normal Sinus Rhythm	14	58.3%	15	62.5%	1.07	0.883
Elevated LFTS (≥40)	4	16.7%	4	16.7%	1	1
Hypothyroidism	6	25.0%	9	37.5%	1.5	0.5
Readmissions per Patient	1.7	±1.4	1.4	±1.3	Diff = 0.3	0.446

Discussion

This single-center, matched cohort study compared patients receiving dronedarone or amiodarone. In terms of the primary outcome of the composite including death, stroke, myocardial infarction and systemic embolism, the two groups had no statistical difference despite 12 events occurring in the amiodarone group and 5 events in the dronedarone group. Likewise, no secondary outcomes produced a statistically significant difference. There was no difference between the two groups in terms of all-cause mortality, stroke, myocardial infarction, systemic embolism. While six amiodarone patients experienced cardiovascular death compared to zero dronedarone patients, the outcome was not significant. The ANDROMEDA and PALLAS trials were both terminated early due to increased mortality of the dronedarone group compared to placebo.[6,7] Because of these trials, the dronedarone group contained no patients with permanent AF and only three patients with symptomatic heart failure. Dronedarone was discontinued in all three heart failure patients in accordance with the contraindications found in the package insert.[5] The clinical process decreases the mortality risk of the dronedarone group by excluding the patients identified to be at a higher risk of death. Meanwhile, the amiodarone patients had a higher rate of heart failure which has a higher risk of mortality and a potentially explains the disparity in mortality outcomes between the two groups.

In literature, amiodarone consistently remains the most effect agent at maintaining normal sinus rhythm at approximately 65%.[2] This study matches the historical results for amiodarone treatment and 62.5% of patients demonstrated efficacy. However, this study found the success of dronedarone at 58.3% compared to the 35% efficacy of the ATHENA trial.[4] These results may not reflect the overall efficacy of dronedarone in patients. This patient population primarily represented those continuing the medication during a hospital admission. Only one patient initiated dronedarone while an inpatient. The majority of dronedarone patients were continuing the medication because they had demonstrated previous efficacy.

As dronedarone was designed to reduce the toxicities associated with amiodarone, this study monitored the common adverse events. Amiodarone is known to cause liver and lung toxicities, and the use of dronedarone is contraindicated in patients that have experienced these complications with prior amiodarone use.[3,5] During the study, no cases of pulmonary toxicity were observed in either group. The rates of liver dysfunction were the same at 16.7% for both groups. The sensitivity of liver dysfunction was set at any elevation of AST or ALT greater than 40 mg/dL. Several of the patients with liver damage were known to be caused by excessive alcohol use and not considered to be due to the

antiarrhythmic agent. Another common amiodarone complication is changes in thyroid metabolism – both hyperthyroidism and hypothyroidism. The rates of hypothyroidism were determined by the diagnosis on the problem list, prescription use of levothyroxine on the medication list, or elevated TSH levels on lab results. The rate of hypothyroidism in the amiodarone group was 37.5% compared to 25% in the dronedarone group. Two dronedarone patients had hyperthyroidism directly related to prior amiodarone use, potentially confounding the results. Similarly, this information correlates the rate of hypothyroidism with the two medications without attempting to establish causality. Patients may have been diagnosed with hypothyroidism prior to the development of AF and not as a result of medications.

Both amiodarone and dronedarone are known to increase the risk of QT prolongation due to the mechanism of action on ion channels in myocardial tissues.[3,5] Both groups demonstrated an elevation of the QTc interval, as 70.8% of amiodarone patients and 37.5% of dronedarone patients had an extended interval at admission. Meanwhile, no cases of Torsades de Pointes were noted during the study timeframe, consistent with the rarity of the complication and the rates of Torsades in patients taking amiodarone and dronedarone.

No differences were found between the rates of readmission between the amiodarone and dronedarone groups. The dronedarone group had slightly more admissions (1.7) compared to the amiodarone group (1.3), but the difference was not statistically significant. These readmissions looked only at admissions and discharges from one year after the patient's first hospital encounter. The reasons for admission were not noted and therefore it cannot be determined if the medications played a role in the need for readmission. However, the amiodarone group average was driven by a single patient with 9 readmissions who died during the final encounter. When that patient is excluded, the amiodarone rate drops to 1.1 ± 0.9, but the difference remains nonsignificant ($p = 0.084$).

This medication use evaluation attempted to compare the outcomes of patients that received dronedarone and amiodarone during an inpatient encounter. Few studies exist directly comparing the two medications, especially in the clinical setting. As a retrospective study, the authors made no attempt to guide prescriber decisions providing generalizability to the results. One limitation to this study is the small sample size. By utilizing the data at a single center during a single year, the number of dronedarone patients was limited. Another limitation could be the matching process which compared age, sex and date of admission. No effort was made to control for severity of disease nor to exclude patients with heart failure. This disparity may have allowed for an amiodarone population with more progressive diseases, however the results remained nonsignificant.

Direct comparisons between dronedarone and amiodarone remain rare. More studies, potentially involving more centers, should measure the mortality and efficacy of current clinical practices. In the current study, several differences were identified between the two groups but each failed to meet statistical significance with a small sample size. An expanded patient population may potentially identify differences in cardiovascular mortality, QTc prolongation, and hypothyroidism.

Conclusion

This single-center, matched cohort study of clinical use of dronedarone and amiodarone during hospital admission found no statistical difference the rates of mortality, stroke, myocardial infarction and systemic embolism. Clinical decision-making which preselects the dronedarone population may prevent the serious potential adverse events in the treatment of AF.

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